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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/673,125	09/25/96	MARKLAND	W	MARKLAND-1B

EXAMINER	
DEGEN N	
ART UNIT	**PAPER NUMBER**
1805	7

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 7/11/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-13 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-13 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

Sequence Information

1. The nucleotide and amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821-1.825 for the following reasons: This application clearly fails to comply with the requirements of 37 CFR 1.821-1.825. Applicants' attention is directed to these regulations, published in 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990. A copy of the "Sequence Listing" in computer readable form has been submitted as required by 37 CFR 1.821(e). However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823. The sequence "glu-ala-ala-glu" at page 22, line 27 of the specification is also subject to the sequence listing requirements. Applicants must provide an substitute computer readable form (CRF) copy of the "Sequence Listing", an substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

3. Claims 4 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. Applicants have not described how to determine which plasma kallikrein inhibiting protein molecules have substantial homology to the native molecule will have the same characteristics or function in the same manner as the protein itself. Nor is it disclosed whether these derivatives that have substantial homology may include mutations, insertions, or deletions at either the nucleic acid or amino acid level. Further, there is no indication of a level of activity which must be obtained in order to have a useful inhibitory protein variant or polypeptide fragment. In addition, **In re Wands**, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations in determining whether or not undue experimentation would be involved in practicing inventions. These factors are: the quantity of experimentation necessary, the amount of direction or guidance needed, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims. The amount of experimentation necessary to determine which protein variants that have substantial homology with the native protein have the same characteristics as the protein itself is beyond the scope of one with ordinary skill in the art. The instant application contains no guidance in performing these

experiments, which adds to the difficulty in practicing the invention. There is no guidance as to which of the numerous algorithms for determining the level of homology is to be used for sequence comparison, nor to the types and placement of alignment of sequences being compared. The examples presented in the specification do not adequately describe how which of the many existing and creatable inhibitory protein variants that have substantial homology with the native protein will be chosen. By its nature, the instant invention is dependent on the ability of the protein to inhibit plasma kallikrein. The prior art cited does not show that the many possible protein variants will function in the same manner as the native inhibitory protein itself. Although the level of skill in the molecular biology art in relation to protein sequencing is very high, the abovementioned factors, in addition to the extreme breadth of the claims, are indicative of extreme unpredictability in reference to the instant invention. When the Wands factors are weighed, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

5. Claims 5, 8 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of diseases related to kallikrein activity, does not reasonably provide enablement for prevention of those disease states. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

6. Applicants have not described how to determine which kallikrein inhibitory protein molecules will completely prevent a condition such as excessive bleeding from causes such as

coagulation defects or surgery. While it is taught that these conditions will be treatable, at least to some extent, by such a kallikrein inhibitory protein, there is no data that they will be completely prevented. In addition, **In re Wands**, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations in determining whether or not undue experimentation would be involved in practicing inventions. These factors are: the quantity of experimentation necessary, the amount of direction or guidance needed, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims. The amount of experimentation and length of time necessary to determine whether a condition is prevented by the administration of a kallikrein inhibitory protein is beyond the scope of one with ordinary skill in the art. The instant application contains no guidance in performing these experiments, which adds to the difficulty in practicing the invention. The examples presented in the specification do not adequately describe how prevention of a disease will be determined. By its nature, the instant invention is dependent on the ability of the protein to prevent excessive bleeding in patients. The prior art cited does not show that these conditions are preventable completely. Although the level of skill in the molecular biology art in relation to treatment of bleeding disorders and problems is very high, the abovementioned factors, in addition to the extreme breadth of the claims, are indicative of extreme unpredictability in reference to the instant invention. When the Wands factors are weighed, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

7. Claims 4, 6-7, 9-10 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of claim 4 is indefinite because, at line 2, it is unclear what is meant by the phrase "substantial homology". Does this mean that any molecule that has any of the amino acids in common is embraced by this claim, or are certain regions of the protein required to be present in order for the molecule to function as claimed? How are insertions, conservative substitutions, and deletions to be accounted for? Is there a certain level of biological activity that must be maintained?

At claim 4, the Sequence ID Nos. of the designated proteins should be inserted into the claim.

At claim 4, line 7, "AND" should be changed to --and--.

At claims 6, 9 and 12, it is not clear where the sample is obtained from, nor how the complex is formed between the protein and the kallikrein. In addition, the process steps should be more clearly set forth.

At claims 7, 10, and 13, there is no clear antecedent basis for the term "analogue". In addition, the process steps should be more clearly set forth.

Double Patenting

8. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the

"right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-5, 8 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 08/208,264. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in the exact mutants claimed.

The '264 patent claims particular kallikrein inhibiting proteins comprising non-naturally occurring Kunitz domains.

The '264 patent does not claim the extent of the mutants claimed in the instant application.

The instant application claims proteins with more extensive mutations. It would have been obvious to one with ordinary skill in the art at the time Applicants' invention was made to make further mutations in a kallikrein inhibiting protein in order to increase the inhibitory activity of the protein, which will enable one to use less protein for either diagnostic or therapeutic purposes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Schnabel ('687 and '481) disclose altered forms of kallikrein inhibitors. The World Patent Applications to Novo Nordisk and the journal article by Girard also disclose mutated kallikrein inhibitors wherein the mutations are different from those claimed in the instant application.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Nancy J. Degen, whose telephone number is (703) 308-3672. The Examiner can normally be reached on Monday-Thursday from 8:00 AM-5:30 PM. The Examiner can also be reached on alternate Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

NANCY DEGEN
PATENT EXAMINER
GROUP 1800

NJD
June 16, 1997